(9)

DRAFT 1

BRAVE PILL: II. PHARMACOLOGICAL TREATMENT/PREVENTION

COL FRANKLIN D. JONES, MD

A. GENERAL CONSIDERATIONS

The development of anxiety, chronic and disabling or acute and overwhelming, has generally been the most significant symptom related to combat breakdown during wars of the 20th Century (Bar-On, et al 1983, Table 1). Furthermore, anxiety may have a noxious effect upon combat efficiency even in those who do not break down. Roberts' (1983) review of Soviet research on anxiety among troops engaged in rigorous exercises closely simulating combat (and possibly involving handling of lethal agents or engaged in actual combat) revealed a vitually linear decrease in combat performance after alleged optimal anxiety levels were reached. The nature of the battlefield is expected to produce anxiety levels exceeding the optimal in all but a small minority of soldiers. The prevention of excessive anxiety or its effective treatment after its appearence, therefore, should have an important impact on combat efficiency.

Jones (1983) has suggested that the ideal drug to treat or prevent combat stress breakdown would be an easily administered, stable compound which would prevent development of or remove anxiety without significant neuromuscular or cognitive impairments, would be non-addictive and would permit an appropriate response to danger. While such a drug is not currently on the market, benzodiazepine (BDZ) receptor studies raise the possibility of developing such a compound.

A non-BDZ drug currently being evaluated as a potential anxiolytic for use by alcoholics, buspirone (trade name Buspar), may have some of these ideal qualities. Studies by Mattila, Aranko, and Seppala (1982) in Helsinki and by Moskowitz and Smiley (1982) in Los Angeles reveal buspirone to relieve anxiety without producing cognitive impairment both in acute and chronic use and even in the presence of alcohol or barbiturates. In fact, buspirone, rather than further decrementing the performance of those under the influence of alcohol, actually appeared to improve psychomotor skills in simulated driving situations. Buspirone is stated to have no more sedation effects than placebo (Feighner, et al 1982) and to have little potential for abuse (Cole, et al 1982).

ERT PILLS (Hegge, Tortella, Tyner)

TARY ISSUES

ltiple situations in which stimulant or depressant cc
nhance effectiveness: sustained ops, surveillance,
casualty management, high-performance weapon systems, etc.

PROBLEMS & HISTORY

a. Poorly understood brain mechanisms

b. Powerful natural arousal mechanisms at work continously; pharmacologic interferance with them may make performance worse rather than better. Natural rhythms and individual variation; larks and owls.

. Past and present arousal/depressant candidates

1. Stimulants
   a. Caffeine
   b. Nicotine
   c. Amphetamines
   d. Go-to-sleep/wake-up routines
   e. Environmental novelty

2. Depressants
   a. Alcohol
   b. Benzodiazepines
   c. Barbiturates

roblems of available stimulants/depressants

. Undesired duration of effects

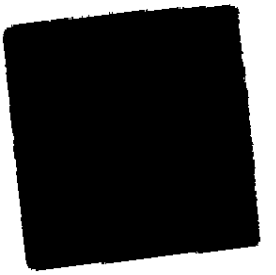
Undesired magnitude of effects

Undesired side effects

Hangover

ls:

Depressant. Nearly universal fatigue during military ops probably eliminates need for long-lasting or powerful depressant. Mild, ultra short-acting drug to nudge system far enough to let natural mechanisms take over would probably be most useful.



2. Stimulant. Ideal drug might have modest peak magnitude, longer duration than depressant. Main issue is elimination of undesired side effects.

3. NEW APPROACHES

a. New benzodiazepines. Large class of drugs; agressive activity by pharmaceutical industry for sleep/anxiety problems.

b. Neuroactive peptides & antagonists. Intensive study in past ten years; likely related to natural control of sleep/alerting processes.

c. Other new classes of chemicals; cyclopyrrolones

Proposed title and topics for output from the Psychopharmacology Study Group (PSG):

The Psychopharmacology of Combat

1. Psychological and Physiological Aspects of Combat Stress (see attached reference)
    a. Psychophysiology of Fatigue
        1) Neuromuscular Fatigue
        2) "Emotional" Fatigue
        3) Sleep Deprivation
    b. Prevention and Treatment of Fatigue
        1) Neurochemical Aspects (Na,K, Lactic Acid, Glucose depletion, etc.)
        2) Circadian Rhythms
        3) Sleep Prophylaxis
    c. Psychophysiology of Anxiety and Fear
        1) Neurophysiology of Activation
        2) Benzodiazepine Receptor Studies
            a) Anxiolytic
            b) Muscle relaxant
            c) Sedative/hypnotic
            d) Anticonvulsant
    d. Prevention or Treatment of Anxiety and Fear
        1) Exposure Models (Habituation)
        2) Relaxation Training
        3) Pharmacological Agents
2. Psychopharmacology of Performance Enhancement
    a. Neuromuscular Tasks
    b. Vigilance Tasks
    c. Cognitive Tasks
    d. Sleep Regulation
    e. Circadian Rhythm Regulation
3. Chemoprophylaxis
    a. Antipanic Drugs
    b. Antiradiation Drugs
    c. Anti-nerve agent Drugs
    d. "Lazarus" Drugs (PGBx)
4. Contents of the Combat Casualty Care Drug Cabinet
    a. Current Psychopharmacological Agents
    b. Proposed Agents
5. Applications of New Technology in Pharmacotherapy and Pharmacoprophylaxis
    a. Recombinant DNA
    b. Computer Programs for Triage of Casualties
        1) Psychological vs Physiological
        2) Chemical vs Radiation Exposure
        3) Prognosis by Symptom Presentation
        4) Type of Chemical Exposure

Franklin D. Jones, MD, COL MC

SMART PILLS

I Human cognitive function very broad - acquisition and retention of fine motor skills aiming & guiding TOW or M16 (endurance pill?) knowledge of facts, (T-72 has 6 roadwheels), knowledge of intellectual skills (encoding/decoding), perception and recognition (guard duty, radar screens, etc) reasoning, inductive & deductive (tactics)

II Goals of a "smart" pill, like others, is not to produce superman, but to ameliorate degradation in cognitive performance induced by such factors as fatigue, anxiety, and/or workload likely to characterize future combat.

III Mechanisms - chemical nature of neural transmission, variety of neurotransmitters, low probability of strict localization - either anatomical or chemical - interaction likely role for all cognitive performances. Knowlwedge of basis of fatigue and anxiety thus crucial to work in this area - introduce classical "stimulants," agents affecting general metabolism, agents affective cerebrovascular function, agents of unknown mechanism.

IV Status Quo

A. "Stimulants" (amphetamine, caffeine)
B. General metobolism agents (TRH, PGBx, Soviet stuff)
C. Agent affective cerebrovascular fuc. (hydergive?)
D. Agents affective known transmitters (l-dopa, choline)
E. Unknown mech - NOO Tropics, peptides, hormones

V Special problems for "smart pills"

A. Trade Offs
B. Ethical sensitivities especially acute here - mind vs body
C. Chronic/tonic use distinction
D. Harder($)to detect interactions with other drugs (legal & illegal)